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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,281	12/11/2000	Marc Mercken	12546.4USC1	3720

7590 04/08/2003

Attention of Mark T. Skoog
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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	20

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/734,281	Mercken et al
Examiner	**Art Unit**
Patricia A. Duffy	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *12-30-02 and 1-21-03*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *20, 21, and 24-30* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20, 21, 24, 29, and 30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *20, 21, and 24-30* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The amendments and responses filed 12-30-02 and 1-21-03 have been entered into the record. Claims 20, 21 and 24-30 are pending.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. This application contains claims 25-28 drawn to an invention nonelected without traverse in Paper No. 13. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections Withdrawn

4. Any rejection not maintained herein are withdrawn in favor of the new rejections set forth below due to Applicants amendments to the claims.

5. The rejecton of claim 22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in veiw of the cancellation of the claim.

6. The rejection of claims 20-24 and 29 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monoclonal antibodies which forms a complex with a phosphorylated peptide YSSPGSPGT (SEQ ID NO:1) or YSSPGSPGT (SEQ ID NO:2) wherein said phosphorylated peptide is phosphorylated at the positions marked with * and specific species thereof, it does not reasonably provide enablement for a monoclonal antibody which ".... forms an immunological complex with any phosphorylated epitope present in a human abnormally phosphorylated tau protein .." variant peptides, or other

phosphorylated epitopes are withdrawn in favor of the new rejections set forth below due to Applicants amendments to the claims.

7. The rejection of claims 20, 23 and 24 under 35 U.S.C. 102(b) as being clearly by Dickson et al (Acta Neuropathol, 73:254-258, 1987 of record in parent prosecution) is withdrawn in view of Applicants amendments to the claims.

8. The rejection of claims 20, 21, 23 and 24 under 35 U.S.C. 103(a) as being unpatentable over Dickson et al (Acta Neuropathol, 73:254-258, 1987 of record in parent prosecution) in view of Kosik et al (Neuron, 1:817-825, 1988) and Binder et al (J. Cell. Biol., 101:1371-1378, October 1985) is withdrawn in view of Applicants amendments to the claims.

9. The double patenting rejections are withdrawn based on the properly filed terminal disclaimers.

Rejections Maintained

Priority

10. The status of nonprovisional parent application(s) (whether patented or abandoned) should be updated. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Claim Rejections - 35 U.S.C. § 112

11. Claims 20, 21, 24, 29 and 30 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention is maintained for reasons made of record for claim 22 in Paper No. 14, mailed 6-26-02.

As to claim 20 and every claim dependent thereon (21, 24, 29 and 30), the limitations in (iii) is unclear because it is unclear what is excluded. For example, the monoclonal antibody is selected to exclude forming an immunological complex with a phosphorylated epitope treated with a desphosphorylating agent. It is unclear if the negative selection is against the phosphorylated epitope or the dephosphorylated epitope. Applicants should make the negative exclusion clear, is the negative selection against the phosphorylated epitope or the resultant treated epitope that would not be phosphorylated ? This issue is still not resolved.

12. Claims 20, 24 and 30 stand rejected under 35 U.S.C. 102(e) as being clearly by Trojanowski et al (U.S. Patent 5,601,985, issued Feb 11, 1997 with priority to August 14, 1991) is maintained for reasons made of record for claims 20, 23 and 24 in Paper No. 14, mailed 6-26-02.

Applicants' arguements have been carefully considered but are not persuasive. Applicants aruge that the T3P antibody of Trojanowski is an antiserum. This is not persuasive, Trojanowski et al specifically teach monoclonal antibodies (see column 2, lines 39-46) against the phosphorylated epitope on tau. The monoclonal antibodies bind the identical phosphorylated epitope as the antiserum and therefore have the identical binding specificity/properties.

13. Claims 20, 24 and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Science, 251:675-678, February 3, 1991) in view of Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) is maintained for reasons made of record for claims 20, 22, 23 and 24 in Paper No. 14, mailed 6-26-02.

Applicants argue that one skilled in the art would not have been motivated to prepare monoclonal antibodies from Lee et al, because at least 7 monoclonal antibodies are disclosed in Lee, one skilled in the art would rather have been guided away from trying to obtain additional monoclonal antibodies. This is not pearuasive, Lee et al teach that the epitope that the T3P antibody binds discriminates normal tau from pathological tau. Lee et al and the art teaches that the other monoclonal antibodies bind A68 (abnormally phosphorylated tau) and normal tau. In contrast to Applicants assertions, one whould have been highly motivated to make monoclonal antibodies to the phosphorylated eiptiope in addition to the motivation explicitly provided by the examiner. "One would have been motivated to make monoclonal antibodies to decrease the lot to lot variability that can happen with polyclonal antisera." Applicants argue that there is no reasonable expectation of sucess for making a monclonal antibody in rat or mouse because of variability of animals to make immune responses to the same immunogen. Applicants cite articles not of record in the 1449 and therefore the assertions based on these references can not be assessed. Applicants argue that quantitative differences in immune responses are noted to specific immunogens. This is not persuasive, if an immune response can be generated a monoclonal antibody can be made, the quantitative difference in a polyclonal response is irrelevant. Any response will allow one to make hybridomas and screen for appropriate monoclonal antibodies secreted therefrom. The skill in this technological area is extremely high and one skilled in the art would have outbred animals to immunize and therefore the strain to strain variation is irrelevant. One would further have a reasonable expectation of success given the number of monoclonal antibodies already made against tau and A68 as reported by Lee et al. Monoclonal antibody manufacture is routine in the art and, in contrast to Applicants' assertions, there is a reasonable expectation of sucess given the demonstrated

immunogenicity of the peptide. At the time that this invention was made, the manufacture of monoclonal antibodies was so routine in the art that textbooks and laboratory guides provided all of the necessary steps. It is noted that applicants own specification provides the same methodology as the art. Applicants have provided no extrinsic evidence that monocloanl antibodies can not in fact be made. Certaintude is not expected by the statue, only reasonable expectation of success. Applicants aruge that even if a hybridoma can be produced, the loss of chromosomes and danger of overgrowth of useful clones is significant and that only a small fraction may produce antibody. This is not persuasive, everything quoted by Applicants is known in the art, routinely accepted as cloning losses and/or controlled for by the art (i.e. cell density). Further, as admitted by Applicants, even given these problems positive clones may be produced. The fraction of the population that these positive clones form is irrelevant, one skilled in the art could screen for the relevant positive clones. Applicants seem to argue that the technology is so unpredictable that one skilled in the art would be unable to make monoclonal antibodies at the time that this invention was filed in 1992. This is not persuasive, the production of monoclonal antibodies was so routine in 1992 that textbooks and laboratory guides were printed to how to routinely make such monclonal antibodies using a demonstrated immunogen.

New Rejections Based on Amendment

14. Claims 20, 21, 24, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a monoclonal antibody that forms a complex with a

phosphorylated epitope present in a human abnromally phosphorylated tau wehrein the monoclaonl antibody is selected to exclude forming in the immunological complex with normal tau proteins, hybridomas and kits claims as depending from the product claims. The specification lacks written description of any monoclonal antibody or any phosphorylated tau epitope that meets this condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification exemplifies the monoclonal antibody AT8 which forms a complex with a phosphorylated peptide YSSPGSPGT (SEQ ID NO:1) or YSSPGSPGT (SEQ ID NO:2) wherein said phosphorylated peptide is phosphorylated at the positions marked with *. This monoclonal antibody has binds a phosphorylated epitope present in a human abnormally phosphorylated tau. However, the art teaches that the AT8 antibody does not in fact have the claimed properties of not forming an immunological complexes with normal tau. Specifically, Goedert et al (Proc. Natl. Acad. Sci.. 90:5066-5070, 1993) that the AT8 monoclonal antibody binds human fetal and newborn rat brain tau, see Figure 1, page 5067. *Clearly, since the AT8 antibody which forms a complex with other human and rat proteins, the specification is not enabled for this specific claim language.* The specification therefore fails to teach how to make antibodies which have the now recited property of forming "....an immunological complex with a phosphorylated epitope present in a human abnormally phosphorylated tau protein .. but selected to exclude...." as now set forth in claim 20. Additionally, since AT8 forms a complex with a phosphorylated peptide YSSPGSPGT (SEQ ID NO:1) or YSSPGSPGT (SEQ ID NO:2) wherein said phosphorylated peptide is phosphorylated at the positions marked with * any other monoclonal antibodies which would also form a complex with a phosphorylated peptide YSSPGSPGT (SEQ ID

NO:1) or YSSPGSPGT (SEQ ID NO:2) wherein said phosphorylated peptide is phosphorylated at the positions marked with *, would also not have the claimed recited properties. Thus, the specification is not enabled for antibodies which have these recited functional properties and does not teach how to make such or describe a monoclonal antibody that binds an abnormally phosphorylated epitope that has such properties. The specification fails to teach other phosphorylated epitopes, which produce antibodies with the recited functional properties. Clearly, the AT8 antibody and similar antibodies which bind this sequence can not have the claimed properties of claim 20. Further, the specification teaches a sole epitope and does not point to other abnormally phosphorylated epitopes on tau with this property. As such, Applicants are not enabled for invention of a monoclonal antibody as is now claimed. In the absence of further guidance from Applicants as to other phosphorylated epitopes bound by monoclonal antibodies which have the claimed functional properties, one skilled in the art would be forced into undue experimentation to make and use monoclonal antibodies with these functional properties.

Applicants' arugments have been carefully considered as they relate to the previous rejection of record but are not persuasive. Applicants argue that fetal and neonatal tau are not "normal tau" in veiw of the teaching of the specificaiton. This is not persuasive, the claims are given the broadest reasonable interpretation in veiw of the art. "Normal" would not be seen to exclude fetal and neonate since these are "normal" conditions. Limitations of the specification are not read into the claim. The AT8 antibody does infact bind "normal tau" with in the conventional meaning in the art. Furthermore, "Normal tau" is not specifically defined in this specification to exclude fetal or neonates.

New Rejections

15. Claim 29 stands rejected under 35 U.S.C. 103 as being unpatentable over Trojanowski et al (U.S. Patent 5,601,985, issued Feb 11, 1997 with priority to August 14, 1991) as applied to claims 20 and 30 above and further in view of Dickson et al (Acta Neuropathol, 73:254-258, 1987) and Catty et al (Antibodies, Volume II A Practical Approach, IRL Press, at Oxford University Press, Oxford, 1990, pages 97-154) for reaons made of record for claim 29, in Paper No. 14, mailed 6-26-02. The rejection is newly applied here because it was origionally made under the incorrect statute.

Applicants arguements have been carefully considered but are not persuasive. Applicants ague that neither Trojanowski et al or Dickson et al teach the monoclonal antibody of amended claim 20. Dickson et al was not relied upon in the combination to provide for the monoclonal antibody of claim 20. The monoclonal antibody of Trojanowski et al binds the same epitope as the antiserum and thus has the same properties absent convincing factual evidence to the contrary. Applicants arguements were not persuasive see response to Trojanowksi et al supra. Further, the references as combined merely provide to an additional second antibody to provide for a sandwich assay of the type of Catty et al. Motivation to combine was provide and the collection of these agents in a kit format to perform an enzyme immunoassay remains obvious.

Trojanowski et al teach monoclonal antibodies that bind to a phosphorylated peptide which corresponds to residues 389-402 of human tau which was selectively phosphorylated at serine position 396, which they term T3P. Trojanowski et al disclose that anti-T3P antibodies were used immunocytochemically to stain tissue sections and in western blot experiments from Alzheimer's disease and control brains where the anti-T3P did not recognize normal tau (page 678, column 1, second paragraph). Trojanowski et al teach that dephosphorylating A68, to which the T3P antibody binds, provides for a drop in

electrophoretic mobility with a treatment with a dephosphorylating agent and migrated to a position very close to that of dephosphorylated tau (page 678, column 2, Figure 2A).Trojanowski et al conclude that A68 is in fact derived from tau (see page 678, column 2, second full paragraph). Trojanowski et al teach test kits for diagnosing a disease comprising antigens capable of binding with antibodies reactive with a peptide comprising the sequence of LysSerProVal wherein the ser is phosphorylated or antibodies specifically reactive with the phosphorylated sequence (see column 8, first full paragraph). Trojanowski et al teach that the identification of abnormally phosphorylated tau can be accomplished by enzyme immunoassay (column 7, lines 40-45).. In particular, Trojanowski et al teach that the identification of abnormally phosphorylated tau can be accomplished by enzyme immunoassay (column 7, lines 40-45) and that kits for use in detecting such are contemplated. Trojanowski et al differ by not explicitly teaching a two site ELISA for detection of abnormally phosphorylated tau and its components in a kit.

Dickson et al teach a second monoclonal antibody binding a second phosphorylated epitope on tau.

Catty et al teach a variety of conventional formats for enzyme immunoassays (see page 103, Figure 2). In particular Catty et al teach the two site immunometric assay as a test for antigen where the capture antibody is attached to a solid phase such as a microtiter plate and the second antibody is labeled (see page 104-105). Catty et al teach all the reagents and buffers needed to perform the ELISA (see page 101, Table 2, page 125 and pages 126-133).

It would have been *prima facie* obvious to measure abnormally phosphorylated tau in a sample by means of a two site indirect ELISA according to Catty et al by substituting the art established monoclonal antibodies of Trojanowski et al and Dickson et al in the method

as a means of detection of abnormally phosphorylated tau because Trojanowski et al teach that the identification of abnormally phosphorylated tau can be accomplished by enzyme immunoassay already in the art and commercially available (column 7, lines 40-45). Further, it would have been prima facie obvious to assemble the all of the necessary reagents (antibody attached to the microtiter plate, buffers, substrates, and developing agents) in a microtiter kit format for convenience and economy for the consumer and to reduce overall processing time for the assay by providing a reduced number of steps (i.e. binding the antibody to the microtiter plate well).

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 20, 21, 24, 29 and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 18, 19 of U.S. Patent No. 6,121,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because the species claimed AT100 anticipates the genus claims recited herein.

Status of Claims

18. All claims stand rejected.

Conclusion

19. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
April 5, 2003

Patricia A. Duffy

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600